CHAPTER

5

Benefits, Risks, and Costs of Screening

This chapter draws from the literature reviewed in the previous three chapters to analyze the impact of a hypothetical prostate cancer screening program for Medicare-age men. In addition, it uses data on Medicare reimbursements to examine some of the economic implications of early detection in this age group. As explained below, the screening benefit analyzed is designed to be illustrative of the difficulties in drawing unambiguous conclusions about the value of screening, rather than to predict the impacts of a screening benefit as it actually would likely be implemented as part of Medicare.

A number of decision models have been published or presented dealing with prostate cancer screening or treatment (58, 124, 195, 196, 217, 316). These models have yielded different results, due to widely different "base case" assumptions about the probabilities and values of the various outcomes of these clinical policies. The lack of definitive data on which to base such assumption, particularly for the effectiveness of treating localized prostate cancer, and the different values different patients may place on potential outcomes make it possible to support analyses of screening that use divergent sets of assumptions.[1]

This paper only considers a one-time screening of men at ages 65, 70, and 75. Realistically, a Medicare benefit would most likely cover periodic screening for example, a digital rectal examination (DRE) and prostate-specific antigen (PSA) every year as the American Cancer Society (ACS) currently recommends, or every two or three years as Medicare currently does for breast and cervical cancer screening respectively. Understanding the true effects of an actual Medicare benefit would also require accounting for the fact that some men would have already received screening before their 65th birthdays. However, as this analysis will demonstrate, current understanding does not allow a definitive assessment of the cost-effectiveness of even a one-time benefit with its relatively simplified set of assumptions, much less a more complex, but realistic periodic benefit.

[1]For example, a recently published paper (30) used one of the decision analyses cited here (124) together with newer, life expectancy data that are more optimistic than those used in the original decision analysis. The authors of the more recent paper conclude that their reanalysis leads to conclusions different from those drawn by Fleming and colleagues. Beck and colleagues, the authors of the newer paper, suggest that radical prostatectomy for localized prostate cancer may actually increase quality-adjusted life-years. These authors also endorse the continuation of randomized clinical trials to resolve issues of cancer progression rates and the ultimate effectiveness of prostate cancer treatment, the two greatest unknowns in the decision about whether to screen for prostate cancer (30).

The analysis is presented in three stages:

- The first stage models the health outcomes of a one-time screening program for three cohorts of 100,000 men 65, 70, and 75 years old respectively using a baseline set of assumptions.
- The second stage adds in the costs of screening, treatment, and associated procedures to estimate the cost-effectiveness of this illustrative one-time screening in terms of dollars life-years gained compared with not screening at all.
- The third stage examines how much these measures of cost-effectiveness change with changes in the assumptions about the effectiveness of treating prostate cancer and other assumptions important to screening.

MODELING THE HEALTH OUTCOMES OF SCREENING

To estimate the health outcomes of a one-time screening program for each of the three age groups, the model follows a hypothetical cohort of 100,000 men. It assumes a certain underlying distribution of prostate cancers of different types. It subjects the men to a combined DRE/PSA screening program (using a 4 ng/mL PSA cutpoint) and follows them with assumptions about diagnostic and treatment strategies as well as the probabilities of the different outcomes of these strategies.

Rather than assign different "values," or "utilities," to nonfatal outcomes such as postsurgical incontinence or metastatic disease, which will be valued differently by different patients (317), the analysis simply records the number of patients with these problems and the life-years over which these problems must be endured, allowing the reader to weigh the risks and benefits of the decision whether to screen. At this stage, the analysis does not downvalue (discount) future years of life, or account for future life-years that would be of lower quality due to disability, loss of independence, or other health problems (225).[2]

The discussion that follows outlines the assumptions used in this model and ties them to the literature review in the preceding chapters. Table 5-1 summarizes these assumptions for 65- and 75-year-old men. All age-specific probabilities for 70-year-old men are the average of the probabilities for those 65 and 75.

Assumptions in the Model

The model employs a Markov process that extends one developed for a published study of the outcomes of treating clinically localized prostate cancer (124).[3] It simulates the clinical course of each cohort of men by allowing them to make transitions from one health state to another in increments of six months. During any six month period, men who harbor prostate cancer in the cohort may present with either local obstruction requiring therapy or develop new metastatic disease. Grade-specific rates of developing metastases come from a patient-level meta-analysis recently conducted by Chodak and colleagues (83).

Probabilities of Prostate Cancer

The model distinguishes among three types of cancer by size: 1) <0.5 mL, all assumed to be contained with the prostate capsule; 2) >0.5 mL with <1 cm of capsular penetration; and, 3) >0.5 mL with >1cm of capsular pen-

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[2]However, the section on cost-effectiveness analysis below appropriately discounts both future years of life and future costs.

[3] A Markov model is a quantitative tool useful in understanding how people move through different states of the world (in this case, states of health) over time when: 1) there are a finite number of states, 2) any individual can fall into only one state in any given time period, 3) the probability of moving from one state to the next over any two periods of time is known, and 4) the periods of time are uniform in length (335). In this analysis, the Markov model describes how many members of each cohort of men experience different types of cancer, treatment complications, other symptoms, and death, when they experience each event, and (as seen later) what costs they incur for Medicare along the way.

TABLE 5-1: BASELINE ASSUMPTIONS USED TO MODEL HEALTH OUTCOMES OF PROSTATE CANCER SCREENING OF MEN AGE 65 AND 75 WITH DIGITAL RECTAL EXAM AND PROSTATE-SPECIFIC ANTIGEN

Assumption	Probability	
	65-year-old men	75-year-old men
Derivation of poor probabilities of prostate cancer		
1. Probability of any cancer = (A)	0.22	0.39
2. Probability of cancer being < 0.5 mL (insignificant, assume all confined) = (B)	0.60	0.60
3. Probability of cancer being > 0.5 mL (significant) with < 1 cm of capsular penetration (intracapsular) = (C)	0.4x0.73=.29	0.4x0.73=.29
4. Probability of cancer being > 0.5 mL (significant) with > 1 cm of capsular penetration (extracapsular) = (D)	0.4x0.27=.11	0.4x0.27=.11
5. Derived prior probability of insignificant (< 0.5 mL) cancer = (AxB)	0.132	0.234
6. Derived prior probability of significant cancer (>0.5 mL), intracapsular = (AxC)	0.064	0.114
7. Derived prior probability of significant cancer (>0.5 mL), extracapsular = (AxD)	0.024	0.042
Probabilities of cancers having different grades		
Insignificant cancers (<0.5 mL)		
8. Well differentiated	0.65	0.65
9. Moderately differentiated	0.26	0.26
10. Poorly differentiated	0.09	0.09
Significant (>0.5 mL) intracapsular cancer		
11. Well differentiated	0.33	0.33
12. Moderately differentiated	0.56	0.56
13. Poorly differentiated	0.11	0.11
Significant (>0.5 mL) extracapsular cancers		
14. Well differentiated	0.04	0.04
15. Moderately differentiated	0.70	0.70
16. Poorly differentiated	0.26	0.26
Derivation of screening results		
17. Probability of a suspicious DRE or PSA requiring biopsy = (E)	0.28	0.40
18. Overall probability of detection of cancer (actual yield) = (F)	0.042	0.072
19. Proportion of detected cancers with insignificant (< 0.5 mL) volume = (G)	0.11	0.11
20. Derived probability of finding an insignificant cancer among men who harbor them = (FxG)/(AxB)	0.035	0.034
21. Probability that screen detected cancers are extracapsular = (H)	0.24	0.40
22. Derived probability of detecting extracapsular cancers among men who harbor them = (FxH)/(AxD)	0.42	0.69
23. Derived probability of detecting significant, intracapsular cancers among men who harbor them =Fx(1-G-H)/(AxC)	0.43	0.31
Probabilities of biopsy complications (with antibiotic prophylaxis)		
24. Urinary tract infection	0.056	0.056
25. Urosepsis	0.005	0.005

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TABLE 5-1: BASELINE ASSUMPTIONS USED TO MODEL HEALTH OUTCOMES OF PROSTATE CANCER SCREENING OF MEN AGE 65 AND 75 WITH DIGITAL RECTAL EXAM AND PROSTATE-SPECIFIC ANTIGEN CONTINUED

Assumption	Probability	
	65-year-old men	75-year-old men
Treatment compliance		
26. Probability of men with confirmed cancer receiving treatment	0.70	0.48
Probabilities of radical prostatectomy complications:		
28. Attributable surgical mortality	0.006	0.006
29. Nonfatal serious cardiopulmonary complications	0.04	0.08
30. Probability of incontinence	0.23	0.23
31. Probability of impotence	0.61	0.61

Assumption	Expected remaining years of life	
	65-year-old men	75-year-old men
Life expectancy (in years)[a]		
32. Without cancer	14.45	8.95
33. With untreated, well-differentiated cancer, < 0.5 mL	14.45	8.95
34. With untreated, well-differentiated cancer, > 0.5 mL	12.64	8.26
35. With untreated, moderately differentiated cancer	12.64	8.26
36. With untreated, poorly differentiated cancer	7.57	6.01
37. With treated intracapsular cancer (< 0.5 mL and > 0.5 mL, all grades)	14.45	8.95
38. With treated extracapsular, well differentiated cancer	12.64	8.26
39. With treated extracapsular, moderately differentiated cancer	12.64	8.26
40. With treated extracapsular, poorly differentiated cancer	7.57	6.01

[a] Metastatic rates for well (> 0.5 mL), moderately, and poorly differentiated cancers derived from G.W. Chodak, R.A. Thisted, G.S. Gerber, et al., "Results of Conservative Management of Clinically Localized Prostate Cancer," *New England Journal of Medicine* 330:242-248, 1994. Metastatic rates for these cancers are assumed not to vary by volume or capsular status (i.e., only by grade), except for well-differentiated cancers < 0.5 mL, which are assumed not to metastasize. See text for details.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no, K3-0546.0. Massachusetts General Hospital, June 30, 1994.

etration. The underlying prevalence of each of these cancers in the population is derived from autopsy data presented in table 2-5 and explained in appendix A. Pathological data from Oesterling's study (263) of 208 nonpalpable, PSA-detected, Stage T1c prostate cancers provide the probabilities of each size of cancer being well differentiated (Gleason Score of 2 to 4), moderately differentiated (Gleason Score of 5 to 6), or poorly differentiated (Gleason Score of 7 to 10) (256).

Screening and Biopsy

The probabilities that screening yields a suspicious DRE or PSA requiring biopsy (table 5-1, line 17) comes from Richie and colleagues' community-based screen-

ing study (279),[4] as do the overall probabilities that screenees will have a cancer detected and the probabilities that cancers detected through screening will not be confined to the prostate gland (table 5-1, lines 18 and 21).[5] The analysis assumes that transrectal needle biopsy (TRNB) is the "gold standard" for confirming or rejecting suspicious DRE/PSA results. In the Richie study, only 69 percent of men ages 60 to 69 with suspicious PSA or DRE results actually received biopsy. For men ages 70 to 79, the biopsy compliance rate is 68 percent. These compliance rates are implicit in the probabilities that screening will detect cancer in both the Richie study and the analysis in this chapter (table 5-1, line 18). The probabilities that detected cancers will be of small volume (< 0.5 mL) come from Oesterling and colleagues' study of the pathology of nonpalpable T1c cancers described above.[6]

Combining these data on screening results with the data on the prior probabilities of harboring cancers allow the estimation of age- and volume-specific sensitivities for a one-time combined DRE and PSA screening (table 5-1, lines 20, 22, and 23).[7]

As indicated in chapter 3, biopsy itself can result in infection even with antibiotic prophylaxis. Assumptions about the rates of infections confined to the urinary tract (16, 89,) and urosepsis (91) are taken from the literature.

Treatment Strategies and Cure Rates

Because biopsy cannot determine the volume, grade, and extent of spread of discovered cancers, this analysis assumes all men found to have cancer are offered aggressive treatment. Based on data from Richie (279), 70 percent of 65-year-old men are assumed to accept that recommended treatment; the analysis assumes a 48-percent compliance rate for 75-year-old men.

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[4]It is interesting to note that the proportion of Medicare-age screenees who would have suspicious results on DRE and PSA testing (28 to 40 percent depending on age) is much higher than for mammography (up to 6 percent) (351), fecal occult blood testing (2 to 5 percent) (348), or Pap smears (1 to 13 percent) (347). Thus, the level of intrusiveness of a strategy of early detection of prostate cancer, with recommendations for biopsy being generated in over a quarter of screenees, is much greater than among other commonly used cancer screening strategies.

[5]These estimates of the age-specific yield of combined DRE and PSA screening, which come from the study by Richie (72, 279), favor screening since the volunteers who participated in the study may have had an enriched prevalence of cancer. As previously noted in chapter 3, a community-based study using the same screening strategy among men ages 40 to 79 found cancer in 5 out of 537 (<1%) screenees (261).

[6]Among prostate-confined cancers, the Richie study (279) does not distinguish between the volume categories used in this analysis (<0.5 mL and >0.5 mL). Hence, this analysis uses Oesterling's 11 percent probability that detected cancers are <0.5 mL (263) even though the Oesterling data are not age-specific. The resulting mix of cancers discovered by screening and coming to radical prostatectomy predicted by the model at age 65 are as follows: <0.5 mL, 11 percent; >0.5 mL and intracapsular, 65 percent; and .05mL and extracapsular, 24 percent. This distribution is actually considerably more favorable than the distribution of T1c cancers coming to radical prostatectomy recently described by investigators at Johns Hopkins University (52, 119): insignificant or "minimal" (<0.5 mL), 26 percent; "moderate" (includes some cancers with capsular penetration if well or moderately differentiated), 40 percent; and "advanced," 34 percent. However, those investigators felt that only tumors less than 0.2 mL with a Gleason grade less than seven were truly "insignificant," and candidates for expectant management; this category comprised 16 percent of their T1c tumors. Oesterling (263), on the other hand, found that only 11 percent of his series of T1c cancers were less than 0.5 mL in volume, and Richie (279) reported that only 24 percent of screen-detected cancers in men this age were unconfined; as indicated, this model reflects Oesterling and Richie's more favorable probabilities.

[7]The model-estimated sensitivities of combined PSA/DRE/biopsy are lower than many clinicians would predict. For example, at age 65, 3.5 percent of cancers less than 0.5 mL, 42 percent of intracapsular cancers >0.5 mL, and 43 percent of extracapsular cancers >0.5 mL would be detected. However, if one assumes full compliance with biopsy for suspicious screening results (instead of 69 percent), the estimated sensitivities of DRE/PSA/biopsy would increase to 5, 60, and 62 percent, respectively. These estimated sensitivities reflect the assumption that cancers are distributed by volume according to the autopsy study by McNeal (233) described in table 2-5 and appendix A. Assuming different distributions of cancers by volume would affect the estimated sensitivities, but would not affect the estimated benefits of screening, which are based on the post-test distributions of cancer reported in screening studies. For example, if only 20 percent, (rather than 40 percent) of prevalent cancers are greater than 0.5 mL in size, as reported in some cystoprostatectomy series (328), the sensitivity of screening at age 65 for cancers less than 0.5 mL would drop to 4 percent, and the predicted sensitivities of DRE/PSA/biopsy (assuming perfect compliance) for intracapsular and extracapsular cancers >0.5 mL would both be over 100 percent. In other words, the yield of cancers >0.5 mL described by Richie (279) would actually be greater than the predicted prevalence of these lesions.

Because there is no evidence from controlled studies that aggressive treatment (by either radical prostatectomy or radiation therapy) reduces the risk of death compared with expectant management, this analysis assumes that men with cancers confined to the prostatic capsule (absence of *complete* capsular penetration *of more than 1 cm*^{2}) are *cured* by aggressive treatment, regardless of other prognostic factors, such as degree of tumor differentiation. This assumption, which is favorable to screening (all else being held equal) is based on the work of Epstein (118), who has documented a worse prognosis for tumors with established, complete capsular penetration, as opposed to partial capsular penetration.[8]

Although there are two strategies for aggressive treatment (radical prostatectomy and radiation therapy), the baseline analysis examines only radical prostatectomy. This initial assumption seems reasonable despite older data that radiotherapy has been more commonly used, as the urologic literature now strongly endorses radical prostatectomy as the best treatment for localized prostate cancer, and because men with suspicious screening tests would almost always see a urologist for TRUS and biopsy. The rapidly rising rates of radical prostatectomy in the United States also support this initial assumption. Assuming equal effectiveness for radiation therapy (in the absence of strong evidence to the contrary) would result in similar estimated benefits; however, estimated risks would be much lower.[9]

Patients who are found to have distant metastases are assumed to receive hormonal therapy. Patients receiving such therapy are assumed to be responsive to it for a period of time, but then enter a "refractory" period characterized by no further benefit as well as pain or other discomfort before dying from the cancer or, infrequently, from some other cause.

All patients with intracapsular cancers (whether >0.5 mL or <0.5 mL in volume) who undergo and survive treatment are assumed to have the same life expectancy they would have had if they never had cancer (14.45 years for 65-year-old men and 8.95 years for 75-year-old men). In addition to the extra years of life they gain, these patients also avoid years of both hormone-responsive and refractory disease and associated morbidity. At the same time, though, they do risk the complications of aggressive treatment as outlined in the next section. Treated patients whose cancers are found to have spread beyond the prostate capsule at time of surgery have the same life expectancy as untreated patients with extracapsular cancer.

Finally, the analysis assumes that following radical prostatectomy, no additional cancer treatment is administered unless patients develop documented metastatic disease (as described below). In fact, in a survey of Medicare beneficiaries, 18 percent of men without metastatic disease reported followup radiation therapy within four years of radical prostatectomy, 10 percent reported hormonal therapy, and 15 percent reported orchiectomy (124). As is the case for primary aggressive treatment, there is no evidence from controlled studies that any such interventions (in the absence of documented metastases, at least) improve patient outcomes. Exclusion of

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[8]Although some men with established capsular penetration and no evidence of the tumor on the outside of tissue removed during prostatectomy (negative surgical margins) may be cured as well, these cases are balanced by Epstein's observation that roughly 25 percent of men with only partial capsular penetration had in fact demonstrated evidence of progression after eight years.

[9]Estimates of the treatment complications that would accrue if all patients were treated with radiotherapy, rather than radical prostatectomy, are presented later.

the costs associated with these additional treatments in the cost-effectiveness analysis later in this chapter reduces the total costs associated with screening, thus generating more favorable cost-effectiveness ratios.

Treatment Complications

Assumptions about the rate of complications following prostatectomy come from the survey of Medicare beneficiaries by Fowler and colleagues (124) since these are the most generalizable data available (see table 4-3). Among these risks, the model uses relatively conservative definitions for incontinence and impotence. Only men who drip more than a few drops of urine every day are considered incontinent[10]; while only preoperatively sexually active men who have had *no* partial or full erections since surgery are considered impotent.[11]

Although pelvic lymphadenectomy has its own complications (229), we assume no complications for this procedure as some clinicians question whether it is necessary at all. The analysis disregards other, less frequent complications of surgery and radiotherapy, such as rectal injury (230).

Prognosis and Life Expectancy

The analysis assumes that prognosis is determined entirely by grade, rather than extent of tumor; that is, a moderately differentiated cancer has the same prognostic impact whether it is intracapsular or extracapsular. The only exception is for well-differentiated tumors less than 0.5 mL in volume, which are assumed not to have potential for metastasis, and hence, equivalent to not having cancer at all.

Table 5-1 details life expectancies for untreated cancers.[12] Age-specific probabilities of death from causes other than prostate cancer used in the model were derived from U.S. life tables (350). Grade-specific rates of developing metastatic cancer come from an individual patient level meta-analysis by Chodak and colleagues (83). These data also generated grade-specific estimates of life expectancy for men with untreated cancers. The impact of treatment on rates of metastasis and these life expectancies are described above.

To model the progression from hormonally-responsive to hormonally-refractory metastatic cancer and the excess mortality associated with advanced prostate cancer, the model incorporates data from a randomized trial of hormonal treatment of late-stage disease (93). The data yield a progression rate to refractory prostate cancer of 36 cases per 100 patient years, and an excess mortality rate from hormonally-refractory metastatic cancer of 80 deaths per 100 patient years.[13]

Men who have prostate cancer are susceptible not only to metastatic disease, but to complications from local progression as well. Obstructive symptoms or bleeding from progression in the prostate may require transurethral resection of cancer tissue for palliation. Men who still have a prostate in place may also eventually re-

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[10]If wearing pads is used to define incontinence, the risk would be higher; see table 4-3.

[11]Excluding consideration of all treatment-related complications other than the two most common ones, impotence and incontinence, is another assumption that favors screening in this analysis.

[12]The analysis incorporates relatively high rates of grade-specific metastatic and cancer-specific death rates in this model; these rates are calibrated to the 10-year cancer-specific survivals reported in Chodak's (83) individual-patient-level meta-analysis, which excluded studies of Stage A1 cancers, which may well be treated aggressively in some patients in the current environment. These metastatic and death rates are favorable to screening. As a result of these assumptions, the model predicts that a 65-year-old man has a cumulative probability of eventually dying of prostate cancer of 4.1 percent, while the empirical epidemiologic evidence documents this risk is 3 percent or less (308, 314). Higher metastatic rates or assignment of metastatic potential to small volume, well-differentiated tumors would cause even greater divergence between the predicted and observed cumulative incidences of prostate cancer mortality.

[13]Median survival in this trial once the disease became hormonally refractory was 0.9 years.

quire transrectal resection of the prostate (TURP) for progressive benign prostatic hyperplasia (BPH). This analysis assumes that radical prostatectomy completely eliminates these risks and their associated costs. Assumptions used to calculate costs of transurethral resection for those men with cancer who do not receive radical prostatectomy are reviewed in the section on costs later in this chapter.

The assumptions about prognosis and cure rates from treatment are particularly favorable to screening; to the extent that relatively more future morbidity and mortality result from cancers that have already spread beyond the prostate (a likely scenario), the benefits of screening will be less impressive. Another way of viewing the impact of these assumptions is through the reduction in the rate of metastases through the treatment patients receive. For well-differentiated cancers, the model predicts a 97 percent decrease in the metastatic rate compared with 70 percent for moderately differentiated, and 56 percent for poorly differentiated cancers.

Net Impact of Assumptions

As indicated in the sections above, many of the assumptions made in this baseline analysis of the health outcomes of a one-time screening benefit are favorable to screening. These include relatively high yields of screening itself, high rates of metastasis and cancer-specific death with untreated cancers, and 100 percent cure rates for treated intracapsular cancers.[14] Given these assumptions, the estimated health outcomes for screening with subsequent aggressive treatment in this baseline analysis probably represent the *maximally attainable* benefits of one-time screening.

Results

Tables 5-2 through 5-4 provide "balance sheets" with baseline estimates of the risks and maximal benefits of a one-time screening of 100,000 men ages 65, 70, and 75 with DRE and PSA. Table 5-5 presents estimates of treatment complications that would accrue if all patients undergoing treatment received radiation therapy instead of radical prostatectomy. These estimates are based on rates of complications reported in the literature and summarized in chapter 4 (362).

The model indicates that a one-time screening would result in a very large number of prostatic biopsies (19,330 to 27,200 per 100,000, depending on age), a small number of surgical deaths (18 to 23 per 100,000), and a larger number of men rendered incontinent (260 to 311 per 100,000), impotent (1,357 to 1,622 per 100,000), or both (405 to 483 per 100,000) as a result of surgical treatment. Because these complications must be endured from the start, a very large number of life-years with these complications are generated by early detection efforts. Over time, using the optimistic assumptions about the efficacy of treatment, 653 men age 65, 570 men age 70, and 427 men age 75 who would otherwise have developed metastatic prostate cancer (542, 449, and 314 of whom would become hormone-refractory and die, respectively) would die of something else first in each of these cohorts of 100,000 screenees. The *net* benefit of

[14]The fact that this part of the analysis does not "discount" future life-years relative to current life-years also favors screening as risks of treatment. Discounting accounts for the fact that future costs and benefits are valued less than the same outcomes encountered in the present. It is particularly significant in the case of prostate cancer screening and treatment since the benefits of treatment (and risks of cancer) are faced in the future, while the risks of screening and treatment are faced in the present. Hence, discounting would diminish the estimated life-years gained through screening. The analysis does discount future health benefits subsequently when examining the costs and cost-effectiveness of screening.

TABLE 5-2: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 65-YEAR-OLD MEN WITH DRE/PSA

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened	78,000	13,200	6,424	2,376	100,000		
Estimated harm							
CA missed by DRE/PSA/biopsy (compliance with biopsy 69%)		12,744	3,743	1,363	17,850		
CA detected by DRE/PSA/biopsy		456	2,681	1,013	4,150		
Suspicious DRE/PSA					28,000		
TRUS/biopsy (compliance with biopsy 69%)					19,330		
Urinary tract infections from biopsy					1,083		
Urosepsis from biopsy					96		
Death from urosepsis					1	(14)[a]	
Radical prostatectomy (compliance with RPX 70%)		320	1,877	709	2,906		
Deaths from radical prostatectomy		2	12	4	18		
Life-years lost from radical prostatectomy deaths		(28)	(167)	(50)		(245)	
Morbidity from radical prostatectomy							
Incontinence:	n affected						
	life-years affected						
Impotence:	n affected						
	life-years affected						
Both incontinence and impotence	n affected						
	life-years affected						
Total harm from screening (life–years)						(259)	(27,510)
Total harm per patient screened (days)						(1)	(100)
Total harm per patient treated (days)						(33)	(3,455)

CONTINUED

TABLE 5-2: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 65-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	**Cancer < 0.5 mL**	**Intracapsular**	**Extracapsular**	**Total number**	**LY saved**	**LY improved**
Estimated maximal benefit							
Survive radical prostatectomy		318	1,865	705	2,888		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		45	608	0	653[b]		
Life–years affected		72	731	0			803
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		38	504	0	542[b]		
Life–years affected		27	260	0			287
Cancer deaths *prevented*		38	504	0	542[b]		
Additional years of life attained		338	4,274	0		4,612	
		Total benefit from screening (life-years)				4,612	1,090
		Total benefit per patient screened (days)				174	
		Total benefit per patient treated (days)				579	137

[a] Life-years and days *lost* through screening are presented in parenthesis.

[b] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA: cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA: Massachusetts General Hospital, June 30, 1994.

TABLE 5-3: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 70-YEAR-OLD MEN WITH DRE/PSA

				Cancer > 0.5 mL				
		No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened		69,500	18,300	8,906	3,294	100,000		
Estimated harm								
CA missed by DRE/PSA/biopsy (compliance with biopsy 69%)			17,674	5,671	1,460	24,805		
CA detected by DRE/PSA/biopsy			626	3,235	1,834	5,695		
Suspicious DRE/PSA						34,000		
TRUS/biopsy (compliance with biopsy 69%)						23,460		
Urinary tract infections from biopsy						1,314		
Urosepsis from biopsy						117		
Death from urosepsis						1	(12)	
Radical prostatectomy (compliance with RPX 59%)			369	1,909	1,082	3,360		
Deaths from radical prostatectomy			2	12	7	21		
Life-years lost from radical prostatectomy deaths			(27)	(140)	(66)		(233)	
Morbidity from radical prostatectomy								
Incontinence:	n affected					301		
	life-years affected							(3,229)
Impotence:	n affected					1,569		
	life-years affected							(16,908)
Both incontinence and impotence	n affected					467		
	life-years affected							(5,050)
			Total harm from screening (life–years)				(245)	(25,187)
			Total harm per patient screened (days)				(1)	(92)
			Total harm per patient treated (days)				(27)	(2,736)

CONTINUED

TABLE 5-3: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 70-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY saved	LY improved
Estimated maximal benefit							
Survive radical prostatectomy		367	1,897	1,075	3,339		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		46	524	0	570[a]		
Life–years affected		67	560	0			627
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		37	412	0	449[a]		
Life–years affected		22	180	0			202
Cancer deaths *prevented*		37	412	0	449[a]		
Additional years of life attained		254	2,765	0		3,019	
		Total benefit from screening (life-years)				3,019	829
		Total benefit per patient screened (days)				113	
		Total benefit per patient treated (days)				328	90

[a] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA: cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA, Massachusetts General Hospital, June 30, 1994.

TABLE 5-4: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 75-YEAR-OLD MEN WITH DRE/PSA

				Cancer > 0.5 mL				
		No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened		61,000	23,400	11,388	4,212	100,000		
Estimated harm								
CA missed by DRE/PSA/biopsy (compliance with biopsy 68%)			22,604	7,843	1,318	31,765		
CA detected by DRE/PSA/biopsy			796	3,545	2,894	7,235		
Suspicious DRE/PSA						40,000		
TRUS/biopsy (compliance with biopsy 68%)						27,200		
Urinary tract infections from biopsy						1,523		
Urosepsis from biopsy						136		
Death from urosepsis						1	(9)	
Radical prostatectomy (compliance with RPX 48%)			382	1,702	1,389	3,473		
Deaths from radical prostatectomy			3	11	9	23		
Life-years lost from radical prostatectomy deaths			(23)	(100)	(71)		(194)	
Morbidity from radical prostatectomy								
Incontinence:	n affected					311		
	life-years affected							(2,597)
Impotence:	n affected					1,622		
	life-years affected							(13,598)
Both incontinence and impotence	n affected					483		
	life-years affected							(4,062)
			Total harm from screening (life–years)				(203)	(20,257)
			Total harm per patient screened (days)				(1)	(74)
			Total harm per patient treated (days)				(21)	(2,129)

CONTINUED

TABLE 5-4: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 75-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY saved	LY improved
Estimated maximal benefit							
Survive radical prostatectomy		379	1,691	1,380	3,450		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		40	387	0	427[a]		
Life–years affected		63	417	0			480
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		30	284	0	314[a]		
Life–years affected		3	38	0			41
Cancer deaths *prevented*		30	284	0	314[a]		
Additional years of life attained		159	1,459	0		1,618	
		Total benefit from screening (life-years)				1,618	521
		Total benefit per patient screened (days)				62	
		Total benefit per patient treated (days)				170	55

[a] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA = cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA, Massachusetts General Hospital, June 30, 1994.

TABLE 5-5: EXPECTED HARM FROM A ONE-TIME PROSTATE CANCER SCREENING (DRE/PSA) OF 100,000 MEN, AGES 65, 70, OR 75, FOR CURATIVE RADIATION THERAPY

Morbidity	Life-years of morbidity
Age 65	
Incontinence	1,385
Impotence	11,275
Both incontinence and impotence	593
Total harm from screening	13,253
Total harm per patient screened (days)	48
Total harm per patient treated (days)	1,664
Age 70	
Incontinence	1,269
Impotence	10,337
Both incontinence and impotence	544
Total harm from screening	12,150
Total harm per patient screened (days)	45
Total harm per patient treated (days)	1,321
Age 75	
Incontinence	1,023
Impotence	8,329
Both incontinence and impotence	438
Total harm from screening	9,790
Total harm per patient screened (days)	36
Total harm per patient treated (days)	1,029

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment." OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

screening in each cohort would be 4,353, 2,774, and 1,415 life-years saved (without discounting) for the 100,000 men ages 65, 70, and 75; or 16, 10, and 5 days per man screened, respectively.

If, in fact, contrary to our initial, "best case" assumptions, aggressive treatment of prostate cancer is ineffective at reducing the rate of distant metastases and death, these cohorts would loose about 200 life-years due to operative mortality and endure over 20,000 life-years with incontinence, impotence, or both. The net benefit predicted by the model is very sensitive to the assumptions regarding the efficacy of treatment. For example, if in this undiscounted analysis the proportion of intracapsular prostate cancers that are cured by aggressive treatment is decreased from 100 to 50 percent, the net days of life saved per patient screened at ages 65, 70, and 75 drops to seven, four, and two days, respectively.

DRE/PSA Together Versus DRE Alone

Many physicians already perform DREs in older men to seek evidence of both prostate and colorectal cancer. What is the *marginal value* of adding PSA to the

DRE? In the recent combined screening described by Richie and colleagues (279), DRE, which was suspicious in 16 percent of men ages 60-69, had a predictive value of 21 percent, yielding cancer in 2.4 percent of the screenees. Adding PSA increased the detection rate to 4.2 percent. Therefore, since the ratio of intracapsular to extracapsular disease was roughly equal (at 3:1) between the DRE-detected cancers and the cancers detected by combination screening, one can assume that roughly 60 percent of the risks and maximal benefits presented in table 5-2 would be accrued by screening with DRE alone. However, such results would only be seen if DRE were performed with a very low threshold to proceed to systematic biopsies for any minor palpable abnormality, an approach not common in current clinical practice. Again, roughly half the cancers detected using this DRE-alone strategy would actually be found in palpably normal areas of the prostate as a result of the systematic biopsies. For men ages 70 to 79 in the Richie study, DRE detected cancer in 3.5 percent of screenees versus 7.2 percent for combined DRE/PSA screening, but a lower proportion of DRE-detected cancers was intracapsular compared with all cancers found by combined DRE/PSA screening (45 percent versus 60 percent). Therefore, about half the risks presented in table 5-4 would be expected to accumulate with DRE screening, accompanied by less than half the maximal benefits.

MODELING THE COST-EFFECTIVENESS OF ONE-TIME SCREENING

The overall costs of a screening program would comprise the upfront costs of the screening tests themselves, subsequent ultrasound (TRUS) exams and biopsies, staging tests, early treatment, and therapy for treatment complications. To the extent that early detection and treatment are effective, savings accrue from averting costs of subsequent treatment of local cancer progression, metastatic disease, and end-stage cancer. Appropriate discounting diminishes the value of these later savings since policymakers or patients in the present would rather realize benefits now than in the future. Moreover, older men treated for prostate cancer, on average, extend their lives an average of 6 (age 75) to 19 (age 65) months (see tables 5-2 through 5-4), given their risks of death from other causes.[15]

Beyond whether or not a prostate cancer screening benefit would result in net costs or savings for Medicare, one can also consider whether the health benefit realized for each extra dollar spent for prostate cancer screening (and subsequent treatment) is more or less than those of screening programs or other services already covered by Medicare. This ratio of a benefit per dollar spent is the "cost effectiveness" of the screening program. This section models the cost-effectiveness of the illustrative, one-time screening benefit examined in the previous section. As indicated earlier, the actual estimates produced in this analysis are unlikely to be the same as those for an actual Medicare benefit since Medicare would most likely cover multiple, periodic screenings rather than a one-time benefit. However, as will be seen, this simplified analysis does illustrate how sensitive the cost-effectiveness of screening is to assumptions about the effectiveness of treating prostate cancer.

Cost Assumptions

The Cost of Specific Resources

To estimate the costs of an early detection program with DRE and PSA among our hypothetical cohorts of

[15]Epidemiologically, cardiovascular disease and other cancers are by far the most likely causes (table 2-1). The costs of these alternative scenarios for death further blunt any savings from averting terminal care costs for prostate cancer.

100,000 men ages 65, 70, and 75, this analysis adopts the perspective of the Medicare program and considers only direct medical care costs.[16] Cost estimates for resource inputs are based on the 1992 Medicare fee schedule and diagnosis-related groups (DRG) reimbursements for relevant hospitalizations.[17] Appendix G details these cost estimates. Tables 5-6 through 5-8 combine these costs for individual resource inputs into low, medium, and high estimates of the costs of different steps in the process of early detection and treatment, respectively. The low, medium, and high estimates reflect uncertainty about how resources would be utilized and billed in actual practice.[18] The analysis discounts all future health care costs and health benefits are both discounted at an annual rate of 5 percent.

Other Cost Assumptions

The analysis assumes the marginal costs for the care of hormonally refractory prostate cancer, compared with all other causes of death, to be $6,260 in the last year of life (in 1992 dollars), based on the work of Riley and colleagues (282).

As indicated earlier, men who have prostate cancer but do not receive a radical prostatectomy are susceptible not only to metastatic disease, but to complications from local progression as well. To estimate the costs associated with transrectal resection (TURP) to treat local cancer progression or BPH, the analysis used the weighted average of the only two empirical estimates of the probability of this phenomenon currently available (176, 366).[19]

Also as explained in a previous section, the analysis excludes the cost of any additional cancer treatment (radiation therapy, hormonal therapy, or orchiectomy) unless patients have evidence of metastatic cancer. This assumption again favors early detection and treatment.

In estimating the costs of treating complications of radical prostatectomy (or radiation therapy), the analysis again makes assumptions favoring early detection and treatment. For patients with sexual dysfunction, we ignore all costs other than for penile implants, and assume that no additional patients require surgery for impotence more than four years after surgery.[20] For men with incon-

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[16]Beyond the costs to the federal government through Medicare, patients also bear the direct and indirect nonmedical costs associated with screening and any detected disease such as travel costs to receive medical care, lost wages, and the anxiety associated with being told they may have cancer on the basis of a suspicious screening test result. In addition, patients or third-party private insurers would bear medical care costs not covered by Medicare.

[17]Continuing changes in Medicare reimbursements for procedures associated with prostate cancer screening and treatment may make these 1992 costs inaccurate predictors of costs in 1995 or in subsequent years (13a).

[18]For example, it is unknown exactly what percentage of men would get a pelvic CT scan or bone scan as part of a staging evaluation, or what percentage of men undergoing radical prostatectomy would be billed under DRG 335 (without comorbidity/complications) versus DRG 334 (with comorbidity/complication). An October 1993 publication by the American Urological Association entitled, "Coding Tips for the Urologist's Office," was helpful in preparing the ambulatory component of these estimates.

[19]Johansson (176) recently updated the outcomes in his Scandinavian series of "watchful waiters" at an annual American Urological Association meeting in San Antonio. At 12.5 years of average followup, 30 untreated cancer patients had required TURP over approximately 1,610 person-years (a rate of 0.019 TURPs per person-year); in 16 men the pathology report showed cancer, while in 14 the diagnosis was BPH. Whitmore (366), on the other hand, found that among men with T2 cancers treated expectantly, 23 patients required 37 TURPs in approximately 803 person-years of followup (a rate of 0.046 per person year); 27 men had cancer in their resected specimens while 10 had only BPH. We use an average of these two rates (a weighted average based on person-years of followup would be closer to that of the larger Johansson study) to calculate the costs of treatment for local progression of cancer and for BPH among men with cancer.

[20]For men treated with radical prostatectomy, the survey of Medicare prostatectomy patients by Fowler and colleagues (127) found that actually 15-percent report postoperative treatment for sexual dysfunction within two to four years after surgery: eight percent with a vacuum device, 7 percent with pharmacologic erection therapy, and 3 percent with a penile implant.

TABLE 5-6: MEDICARE COST ESTIMATES FOR EARLY DETECTION AND STAGING OF PROSTATE CANCER USING DIGITAL RECTAL EXAMS AND PROSTATIC-SPECIFIC ANTIGEN

	Low estimate	Mediumestimate	High estimate
Initial testing			
PSA	$30	$45[a]	$60[a]
DRE	$0	$3	$28[b]
Total	$30	$48	$88
Work-up for suspicious results			
Consult (urology)	$47	$47	$47
TRUS (diagnostic)	$0	$85	$85
TRUS-guided biopsy	$189	$189	$189
Pathology (level IV)	$208[c]	$312[d]	$312[d]
Total	$444	$633	$633
Staging for men with cancer			
Pelvic CT scan[e]	$71 (25%)	$142 (50%)	$213 (75%)
Bone scan[e]	$46 (25%)	$92 (50%)	$138 (75%)
Lymphadenectomy[e]	$0 (0%)	$164[f] (25%)	$328[f] (50%)
Visit to discuss results	$28	$28	$28
Total	$145	$426	$707

[a] Assumes some repeat testing necessary.
[b] Assumes brief office visit specifically for a prostate evaluation.
[c] Four cores examined.
[d] Six cores examined.
[e] Not all patients get pelvic CT scan with contrast (cost $284), bone scan ($184), or lymphadenectomy ($656); figures in parentheses indicate percentage of men who get these studies.
[f] Includes pathology fee (level IV, two sets of nodes).
KEY: CT = computed tomography; DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

tinence, the analysis includes only the costs of an artificial sphincter implantation for the six percent of men who reported corrective surgery for incontinence, ignoring the costs of pads for the 31 percent of prostatectomy patients who report using them (124). While some of these men may have had less aggressive and expensive corrective surgery for incontinence (such as collagen injections), the other cost assumptions make the overall approach to estimating costs of treatment complications conservative.

For men with urethral strictures following radical prostatectomy, the analysis assumes that 95 percent are treated with a simple stricture dilation in the office, while only 5 percent need in-hospital operative repair. We assume no additional treatments are required beyond

TABLE 5-7: MEDICARE COST ESTIMATES FOR PROSTATE CANCER TREATMENT

Treatment	Low estimate	Medium estimate	High estimate
Radical prostatectomy			
Hospital[a]	$5,867	$6,271	$6,675
Surgeon	$1,497	$1,497	$1,497
Anesthesia	$194	$194	$194
Pathology[b]	$125	$125	$125
Total	$7,680	$8,084	$8,488
External beam radiotherapy			
Course	$3,604	$3,604	$3,604
Monitoring post-treatment (annual cost)			
Office visit and PSA	$59	$59	$59
Bone scan[c]	$0	$46	$92
Total	$59	$105	$151
Diagnosis and treatment:			
Metastatic disease			
Bone scan	$184	$184	$184
Orchiectomy	$4,406	$4,406	$4,406
Hormonal therapy[d]	$4,224	$5,748	$6,953

[a] Low estimate: 0% diagnosis-related groups 334 (complications) at $7,483 and 100% DRG 335 (no complications) at $5,867; medium estimate: 25% DRG 334 and 75% DRG 335; high estimate 50% DRG 334 and 50% DRG 335.

[b] Level VI.

[c] Low estimate: 0% get bone scan each year at $184, medium estimate: 25% get bone scan each year; high estimate: 50% get bone scan each year.

[d] Annual cost; low estimate: 100% GnRH agonist and 0% flutamide; medium estimate: 100% GnRH agonist and 50% flutamide; high estimate: 100% GnRH agonist and 100% flutamide; includes monthly fees for an office visit ($29) with chemotherapy injection ($4).

KEY: DRG = diagnosis-related groups; PSA = prostate-specific antigen.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

four years after surgery,[21] and ignore costs related to the diagnosis of strictures, such as for cystourethroscopy.[22]

Incorporation of Costs in the Screening Model

The analysis estimates cost-effectiveness by incorporating the costs for early detection, staging, treatment of clinically localized cancer, diagnosis of metastatic disease, and treatment of metastatic disease by orchiectomy, into the Markov model of prognosis described earlier in the chapter. The model accumulates these costs (with appropriate discounting) as each intervention is

[21] Since strictures are often recurrent, this assumption is particularly conservative.

[22] In Medicare survey (127), 20 percent of men reported at least one dilation or surgical procedure for what they believed to be strictures two to four years following radical prostatectomy; 11 percent required treatment at least twice.

TABLE 5-8: MEDICARE COST ESTIMATES FOR THERAPY OF PROSTATE CANCER TREATMENT COMPLICATIONS

	Low estimate	Medium estimate	High estimate
TURP for BPH or local progression of cancer			
Hospital[a]	$2,778	$3,069	$3,361
Surgeon	$898	$898	$898
Anesthesia	$147	$147	$147
Pathology	$92	$92	$92
Total	$3,915	$4,206	$4,498
Treatment for cancer therapy complications			
Incontinence			
(Artificial sphincter)	—	$8,080	—
Impotence			
(Penile implant)	—	$11,350	—
Stricture			
(Dilation)	—	$51	—
(Urethroplasty)	—	$5,259	—

[a] Low estimate: 0% DRG 336 (complications) at $3,943 and 100% DRG 337 (no complications) at $2,778; medium estimate: 25% DRG 336 and 75% DRG 337; high estimate 50% DRG 336 and 50% DRG 337.

KEY: BPH = benign prostatic hypertrophy; DRG = diagnosis-related group; TURP = transurethral resection of the prostate.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

encountered. The model accumulates ongoing costs, such as post-treatment surveillance and androgen deprivation therapy for metastatic disease, continuously with each Markov cycle patients spend in a particular state.

Cost-Effectiveness Results

Tables 5-9 through 5-11 present estimates of discounted costs (in dollars), discounted effectiveness (in life-years saved), and cost per life year saved for cohorts of 100,000 men ages 65, 70, and 75 receiving a hypothetical, one-time screening under the baseline assumptions described in this chapter. Using the medium set of assumptions about costs, the cost per year of life saved (compared with doing no screening) would be $14,200 at age 65, $25,290 at age 70, and $51,290 at age 75.

Sensitivity of the Results

These results are extremely sensitive to the assumption about the effectiveness of prostate cancer treatment and, to a somewhat lesser degree, the assumption about the rate at which cancers of different grades metastasize. As indicated earlier, the actual effectiveness of treatment is unknown because of the lack of randomized controlled trials. Similarly, the true rates of future metastasis and prostate cancer death from tumors currently discovered by early detection are also unknown. The assumptions about both treatment and metastasis used in the baseline

TABLE 5-9: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 65)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	3.045	4.341	4.341
Staging	0.602	1.087	1.573
Treatment	22.578	23.751	24.924
Delayed costs			
Monitoring	2.509	4.457	6.383
Future treatment[b]	-5.929	-9.128	-14.808
Total	$25.804	$29.308	$31.214
	Discounted life-years saved		
Marginal effectiveness	2064	2064	2064
	Dollars per life-year		
Marginal cost-effectiveness	$12,502	$14,200	$15,123

[a] Both future costs and health benefits are discounted at 5% annually.
[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia (BPH), metastatic prostate cancer, and therapy complications.
KEY: TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

analysis are favorable to screening. What happens when these assumptions are relaxed?

- Reducing the grade-specific metastatic rates in this model[23] to those used in the previously published analysis of prostate cancer treatment by Fleming and colleagues (124), the estimate of cost per year of life saved (discount rate 5 percent) ranges from $42,590 at age 65 to $177,094 at age 75.
- Alternatively, assuming only half (rather than all) intracapsular cancers >0.5 mL are cured by radical prostatectomy, the cost per year of life saved ranges from $30,524 at age 65 to $109,721 at age 75 (same discount rate).
- Assuming that both the lower metastatic rates from the Fleming analysis and the lower proportion of cures represent the true state of affairs, the cost per year of life saved would range from $94,458 at age 65 to $506,909 at age 75.

[23] As mentioned earlier, the rates used in this analysis result in a lifetime cumulative risk of prostate cancer death more than a third higher than the risk actually observed in the literature.

TABLE 5-10: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 70)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	4.462	6.362	6.362
Staging	0.826	1.492	2.158
Treatment	26.114	27.472	28.829
Delayed costs			
Monitoring	2.522	4.478	6.407
Future treatment[b]	-5.596	-6.165	-10.531
Total	$31.765	$36.467	$39.042
	Discounted life-years saved		
Marginal effectiveness	1,442	1,442	1,442
	Dollars per life-year		
Marginal cost-effectiveness	$22,059	$25,290	$27,076

[a] Both future costs and health benefits are discounted at 5% annually.
[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia, metastatic prostate cancer, and therapy complications.
KEY: DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

To emphasize the sensitivity of the results to these key assumptions, figures 5-1 through 5-3 display the estimated cost per year of life saved for men ages 65, 70, and 75, using higher (83) and lower (362, 124) metastatic rates, and different assumptions about the proportion of intracapsular cancers (of all grades) cured by aggressive treatment.[24]

Another assumption in the baseline analysis is that the metastatic rate is the same for each grade of tumor (except for well-differentiated cancers less than 0.5 mL in volume), regardless of whether the tumor is intracapsular or extracapsular. If, however, future metastatic events are *preferentially* generated from extracapsular cancers, a likely scenario, the estimated effectiveness of treatment and screening would diminish considerably. For example, if intracapsular cancers have the grade-specific prostate cancer mortality rates described by Fleming (124), while extracapsular cancers have the

[24]The costs per year of life saved are displayed on a log scale because of the steep escalation in costs as the favorable initial assumptions are relaxed.

TABLE 5-11: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 75)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	6.019	8.581	8.581
Staging	1.049	1.896	2.742
Treatment	26.991	28.394	29.797
Delayed costs			
Monitoring	2.208	3.919	5.601
Future treatment[b]	-5.596	-6.165	-10.531
Total	$33.671	$41.424	$44.990
	Discounted life-years saved		
Marginal effectiveness	808	808	808
	Dollars per life-years saved		
Marginal cost-effectiveness	$41.690	$51.290	$55.705

[a] Both future costs and health benefits are discounted at 5 % annually.

[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia, metastatic prostate cancer, and therapy complications.

KEY: DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

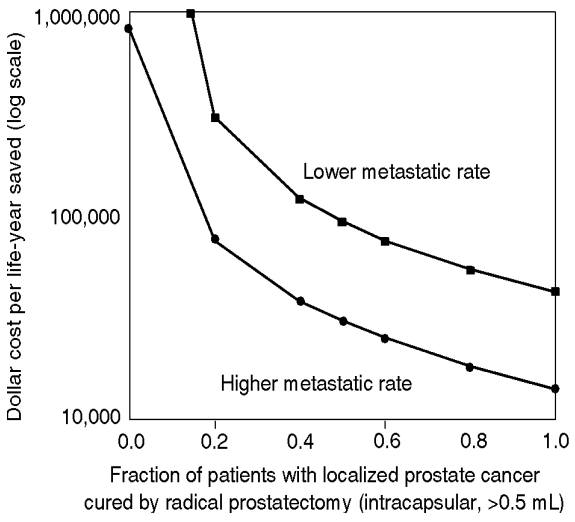
SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

mortality rates described by Chodak (83), the cost-effectiveness estimates for early detection (which are based on the curability of the *intracapsular* lesions) would follow the higher curves in figures 5-1 through 5-3.[25]

Finally, a substantial component of the estimated net benefits come from the early detection and treatment of well-differentiated prostate cancers greater than 0.5 mL in volume. This finding is due to well differentiated cancers having had the same cancer-specific death rates as moderately differentiated cancers in the Chodak (83) meta-analysis. However, Kolon (194) has recently found that men with well-differentiated cancers treated expectantly among cases reported to the Connecticut tumor registry had the same life expectancy as age-matched men in the general state population. If, in fact, well-differentiated prostate cancers do not result in a higher-than-expected future mortality for men diagnosed at age 65 or above, the estimated number of deaths averted per

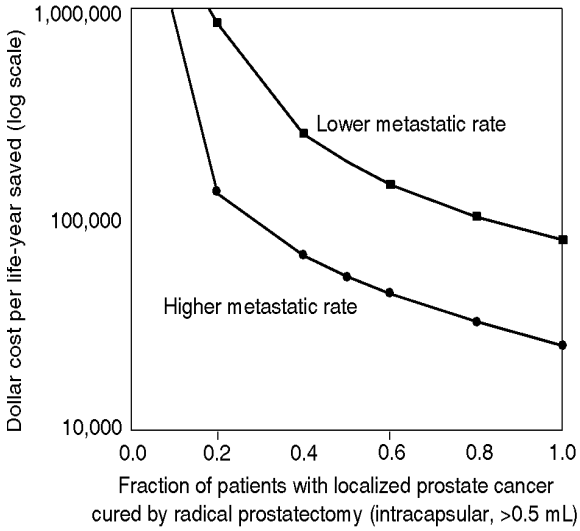
[25]This set of assumptions actually results in a prediction of the cumulative probability of a prostate cancer death for men age 65 of 2.5 percent, within the empirically observed probability range of 2.5 to 3 percent.

FIGURE 5-1: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 65-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

FIGURE 5-2: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 70-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

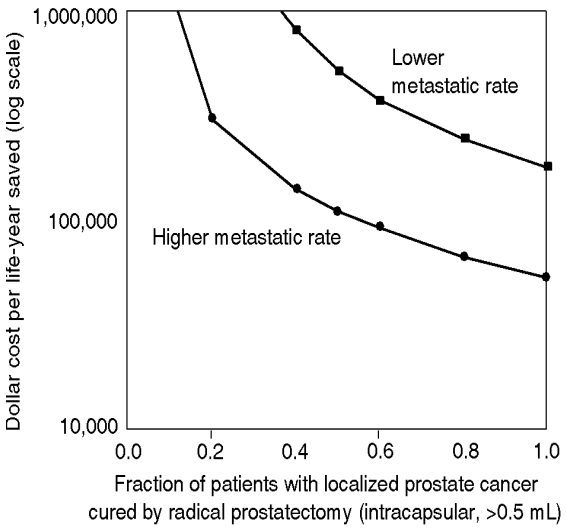
100,000 by screening and treatment (as presented in tables 5-2 through 5-4) would drop from 547 to 414 at age 65, from 431 to 325 at age 70, and from 294 to 224 at age 75. This would result in a parallel increase in the cost per life-year saved by screening.

Turning from effectiveness to cost, how would changes in the cost assumptions affect the cost-effectiveness ratios? Each increase of $10,000 in the costs of caring for terminal prostate cancer above the baseline estimate reduces the present value per person cost of prostate cancer screening only by about $30. This relatively small effect on the analysis is due in large part to the discounting of these future expenses.

Comparisons to Other Medicare Disease Screening

How do these estimates for the cost-effectiveness of one-time screening for prostate cancer compare with previously published estimates for other cancer screening maneuvers among Medicare patients? Such comparisons are problematic since most cost-effectiveness analyses of disease screening for Medicare beneficiaries examine periodic screening rather than only a one-time benefit. However, as part of a previous analysis by the Office of Technology Assessment (OTA), Muller and colleagues (347) found that a one-time screening with cervical Pap smears at age 65 would cost $1,666 per life-

FIGURE 5-3: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 75-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

year saved.[26] Among previous OTA analyses of disease screening for Medicare beneficiaries that examined periodic screening (as opposed to one-time screening) are two that make estimates for colorectal and breast cancer screening. The breast cancer study concluded that annual mammography would cost Medicare $13,200 per year of life saved (346), and the colorectal cancer study estimated that annual occult blood testing beginning at age 65 would cost $35,054 per year of life (348).[27] Medicare currently covers both cervical and breast cancer screening as periodic benefits.

IMPLICATIONS FOR MEDICARE

What information does the analysis in this background paper yield for policymakers considering coverage of prostate cancer screening as a Medicare benefit?

Although the quantitative analysis in this chapter focused on a hypothetical one-time benefit instead of the periodic benefit more likely to be considered by the Medicare program, it does offer important information for policymakers. Most importantly, the cost-effectiveness of any Medicare prostate cancer benefit is extremely sensitive to whether or not treatment of tumors that have not yet spread extends life or not. The analysis suggests that prostate cancer screening could prove to be as cost effective as other disease screening services already covered by Medicare.

On the other hand, if treatment proves to be less than 100 percent effective (or if rates of metastasis turn out to be less than those assumed in our baseline analysis), prostate cancer screening could end up costing much more per life-year saved than other Medicare disease screenings. At the same time, however, screening carries significant risks of complications. These include the possibility of surgical death in at least six out of 1,000 cases, urinary stricture, heart and lung disease, and years of impotence and incontinence in substantial portions of treated patients.

[26]This study also found that the cost per life-year rose as the screening frequency increased. It was $1,453 for screening every five years compared with no screening, was $5,956 per life-year saved when moving from a five-year to a three-year screening cycle, and was $39,693 for annual screening compared with screening for every 3 years.

[27]A more recent analysis of breast cancer screening found that a one-time mammography for Medicare-age women cost $23,212 per year of life saved at ages 65 to 69 and $27,983 per year of life saved at age 70 to 74 (224).

The evidence of effectiveness and cost-effectiveness of other preventive services already covered by Medicare (e.g.. breast and cervical cancer screening, influenza and pneumococcal vaccines) is substantially stronger than for prostate cancer screening. Although scientific knowledge is currently limited as we await the completion of well-controlled clinical trials, the consequences of prostate cancer and its treatment remain serious. Under such circumstances, an informed and reasonable patient could equally well decide to have screening or forgo it. Patient preferences are also a major component in deciding what to do when screening uncovers a localized cancer. Hence, each patient, in consultation with his physician, must use his own values to weigh the potential benefits of screening against the risks of incontinence, impotence, and other adverse reactions that may result from treating those localized cancers discovered through screening.

Given the state of current knowledge about prostate cancer, it may be reasonable for Medicare to consider reimbursement of the screening test. Reimbursement could be seen as ensuring that out-of-pocket screening expenses (however small) not impede well-informed discussion and decisionmaking between physician and patient. Such a Medicare screening benefit could be unrestricted as are similar benefits for cervical and breast cancer screening. However, an unrestricted, permanent benefit might imply that science actually has established the benefit of early detection. An alternative would be to offer it on a temporary basis subject to reconsideration as evidence from clinical trials about the effectiveness of screening and treatment becomes available. Such a benefit could also be coupled with efforts by the federal government to involve as many patients as possible in effectiveness research and to ensure patients and physicians are well-informed about potential benefits and risks of treating cancers uncovered by screening. When data from well-controlled trials (including those described in appendix H) tell us if treating prostate cancer is effective, science will be able to provide more definitive guidance in facilitating clinical decisionmaking for patients and in establishing or continuing a screening benefit under Medicare.